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The Clinical Presentation and Immunology of Viral Pneumonia and Implications for Management of Coronavirus Disease 2019

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Objectives: This review will briefly examine the clinical presentation and important immunology of viral pneumonia with a focus on severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019).

Data Sources, Study Selection, Data Extraction, and Data Synthesis: The most relevant, original and review literature were assessed for inclusion in this review. Sources included the Centers for Disease Control and Prevention, World Health Organization, and PubMed.

Conclusions: Pneumonia is a leading cause of hospitalization and death worldwide, with viral etiologies being very common. Given the rapidly emerging pandemic associated with the novel severe acute respiratory syndrome coronavirus 2 causing coronavirus disease 2019, it is important to review the clinical presentation and immunologic changes associated with viral pneumonia. Symptoms of viral pneumonia include common respiratory tract infection symptoms of cough, fever, and shortness of breath. Immunologic changes include up-regulation of airway pro-inflammatory cytokines and pathogen- and damage-associated molecular patterns contributing to cytokine and genomic changes. Coronavirus disease 2019 clinical presentation is typical of viral pneumonia with an increased prevalence of early pulmonary infiltrates and lymphopenia. Principles of early coronavirus disease 2019 management and isolation as well as potential therapeutic approaches to the emerging pandemic are discussed.

Key Words: coronavirus; immunology; influenza virus; severe acute respiratory syndrome; viral pneumonia

Pneumonia is the leading infectious cause of hospitalization among adults and children in the United States (1). According to the World Health Organization (WHO), lower respiratory tract infection is among the top causes of death globally (2). The Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community study estimated prevalence of pneumonia-related hospitalizations among adults older than 50 to be 4–25 times higher than those 18 to 49 years old (3).

Viral infections are the leading cause of community-acquired pneumonia (CAP) and are an important source of morbidity and mortality. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly discovered virus causing coronavirus disease 2019 (COVID-19) that is responsible for an emerging pandemic. Given the rapid spread of this virus and its association with severe pulmonary disease, the purpose of this review is to provide an overview of the presentation and immunology of viral pneumonia, principles of early management, and application to COVID-19.

CLINICAL PRESENTATION OF VIRAL PNEUMONIA

According to the CDC, the prevalence of CAP is highest among adults 65 to 79 years old (4). Hospitalization among adults is highest in elderly patients (≥ 65 yr) and those with preexisting obstructive lung disease or other cardiopulmonary disorders (4, 5). The most common cause of community- or hospital-acquired pneumonia in adults is viral with the most frequently detected pathogen being human rhinovirus, followed by influenza (9–15% and 4–6%, respectively) (4–8). Other commonly detected causes of viral pneumonia include adenovirus, conventional coronaviruses, human metapneumovirus (HMPV), respiratory syncytial virus (RSV), and parainfluenza. The prevalence of viral respiratory illness is temporal in North America, with peaks of

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influenza, HMPV, and RSV normally seen in the winter months (**Table 1**) (1).

The clinical presentation of viral pneumonia does not differentiate between the specific viral causes of respiratory infection. The common clinical presentation of acute viral respiratory infection includes cough, dyspnea, fever, and pleuritic chest pain. Viral etiologies of lower respiratory infection are less likely to cause sputum production, and if present, tends to be watery or scant. In contrast, sputum production tends to be mucopurulent when due to bacterial pneumonia (8, 9). Clinical signs of viral respiratory illness include fever, rales (crackles) on auscultation, hypoxemia, and tachycardia. These four signs together have a positive predictive value of 57.1%, with fever as the strongest clinically predictive sign of a viral respiratory infection versus that of bacterial etiology (10). Typically, patients with viral pneumonia also will present with a normal leukocyte count and bilateral pulmonary infiltrates on chest radiograph (9). Severe viral pneumonia can manifest as sepsis and respiratory distress requiring intensive care (11). In many moderate to severe cases of pneumonia, hypoxemia occurs from impaired alveolar gas exchange (12), often necessitating mechanical ventilation.

Biopsies in pneumonia are not routinely performed due to the lack of diagnostic, prognostic, and treatment value. However, since influenza has caused the most viral respiratory epidemics to date, a number of studies have examined infected patient's lung biopsy specimens (13). Biopsies obtained during influenza infection reveal a wide range of pathologies, including alveolar edema and exudate, interstitial inflammatory infiltration, and ulceration of bronchial mucosa to type II cell metaplasia (14, 15). In autopsy specimens from H1N1 influenza patients, the respiratory tract exhibited tracheitis, bronchitis, diffuse hemorrhagic alveolar damage, and inflammatory infiltration of alveolar ducts and alveoli (16, 17).

IMMUNOLOGIC CHANGES ASSOCIATED WITH VIRAL PNEUMONIA

The host response to severe viral lung infection occurs secondary to immune dysregulation leading to lung injury and the systemic inflammatory response. There have been many studies on the immunologic changes associated with influenza A virus (IAV). However, little is known about other respiratory viral illnesses in adults. Therefore, much of our discussion on the immunology of viral pneumonia will focus on IAV studies.

Cytokines

During a respiratory infection, airway epithelial cells, natural killer (NK), and CD8 T-cells release interferon-gamma (INF-γ) to limit viral replication (18, 19). There is additional release of interleukin (IL)–6 and IL-8, important mediators of tissue damage and associated with disease progression, respectively (20). High levels of IL-17, tumor necrosis factor (TNF)–α, INF-γ, and IL-4 have been found in postmortem human lung tissue after severe IAV (21).

Although there seems to be a difference in cytokine response based on the cause of respiratory infection, there are mixed results

TABLE 1. Characteristics of Common Respiratory Viruses

Virus	Nucleic Acid Type	Transmission	Seasonality in the United States	Prevention	Available Treatments
Influenza virus	RNA negative ss	Large, aerosolized droplets	Winter	Seasonal influenza vaccine	Oseltamivir, zanamivir, amantadine
Rhinovirus	RNA positive ss	Aerosols, fomites	Throughout	Standard contact precautions	Symptomatic
Coronavirus (e.g., severe acute respiratory syndrome coronavirus, Middle East respiratory syndrome coronavirus)	RNA positive ss	Large aerosolized droplets, fomites	Spring and winter	Standard contact precautions	Symptomatic
Adenovirus	DNA double stranded	Aerosols, fomites	Throughout	Standard contact precautions, oral vaccine approved for U.S. military personnel only	Symptomatic; ribavirin can be used, but no proven clinical data to date
Human metapneumovirus	RNA negative ss	Large droplets, fomites	Spring and winter	Standard contact precautions	Symptomatic; cidofovir or ribavirin can be used, but no proven clinical data
Respiratory syncytial virus	RNA negative ss	Large droplets, fomites	Winter	Standard contact precautions	Symptomatic; ribavirin can be used in severe illness and immunocompromised patients
Parainfluenza virus	RNA negative ss	Large droplets, fomites	Throughout	Standard contact precautions	Symptomatic

ss = single stranded.

in the utility of plasma cytokine levels for prediction of pneumonia etiology (22, 23). In a recent single-center study, differences in admission plasma levels of IL-6, IL-10, IL-17A, and INF-γ were observed between different etiologies of CAP, with INF-γ most elevated in viral CAP (24). Conversely, a similar study demonstrated, admission plasma cytokine levels were not statistically different based on etiology (bacterial vs viral vs mixed bacterial-viral vs unknown etiology) (25). Other studies noted that serum transforming growth factor-beta (TGF-β) levels predicted viral pneumonia, as opposed to other etiologies of CAP, where TGF-β had negative correlations with the Sequential Organ Failure Assessment score in patients that progressed to sepsis (26, 27). Therefore, although the specific cytokine profile elicited by particular viruses is unknown, it is clear that, as with most etiologies of sepsis, an elevation of both pro- and anti-inflammatory cytokines are responsible for the host septic and systemic inflammatory response syndrome response in all severe viral cases of pneumonia (23, 28–30).

Pathogen-Associated Molecular Patterns and Damage-Associated Molecular Patterns

As with many other responses to infection, it is pertinent to recognize the role of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) in viral respiratory infection. Pattern recognition receptors on respiratory epithelial cells, such as Toll-like receptors (TLRs), detect evolutionarily conserved microbial ligands, or PAMPs (31, 32). Viral PAMPs are typically viral envelope proteins or nucleic acids motifs within the DNA or RNA genomes of the virus, which are critical for structure and function (33). The recognition of viral PAMPs leads to transcription and release of type I interferons (33) which effect decreased expression of viral proteins and replication, enhance antigen presentation and NK cell function, and augment adaptive immune responses. Additional recognition of host cell constituents from damaged or dying cells, recognized as DAMPs, are thought to control the magnitude of the immune response (34–36). Together, PAMPs and DAMPs play a major role in the initiation of both the innate and adaptive immune response to viral lung infection (31, 35, 37–40).

Increased Susceptibility to Secondary Bacterial Infection/Ventilator-Associated Pneumonia

Viruses can be the primary cause of pneumonia, present in conjunction with bacterial pneumonia, and/or contribute to increased susceptibility to secondary bacterial infection. In addition to influenza, other viruses, such as rhinovirus, can cause severe pneumonia requiring mechanical ventilation, however, this usually occurs in the elderly and immunocompromised (8, 41). Severe pneumonia associated with noninfluenza viruses is also significantly associated with bacterial coinfection (8, 42–44), most commonly due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Haemophilus influenzae* (45, 46).

A pattern of dysregulated inflammation caused by viral respiratory infection leads to this increased susceptibility to secondary bacterial pneumonia or coinfection. Most research on viral-bacterial respiratory coinfection has been focused on elucidating the pathophysiology of influenza viruses given its high propensity to cause pandemics and higher mortality when compared with the other viruses (13). Influenza A causes a reduction in murine alveolar macrophages and dysregulation of remaining macrophages and neutrophils, one of the body's primary defense mechanisms against bacterial pathogens (47–49). Additionally, prior infection with influenza virus attenuates bacterial induced release of IL-17 leading to decreased innate T cell-mediated bacterial clearance (49). Replication of IAV in respiratory epithelium impairs mucociliary clearance, allowing for increased bacterial colonization (34, 50, 51). Additionally, there is evidence of sustained desensitization of TLR ligands following viral infection, leading to decreased chemokine release and nuclear factor kappa B activation in macrophages (52, 53). This in turn results in attenuated neutrophil recruitment, further decreasing the ability to reduce bacterial load in secondary bacterial infection (52, 53).

Genomic/Transcriptomic Changes Associated With Viral Pneumonia

Although CAP remains a significant source of morbidity and mortality, very little work has been done establishing genomic, epigenetic, or transcriptomic changes specifically associated with viral pneumonia (54). In particular, no clear polymorphism definitively raises the risk of viral pneumonia, limiting personalized medicine for predictive models. In one of the few studies of transcriptomics in viral pneumonia, microarray analysis and Ingenuity Pathway Analysis (Qiagen, Redwood City, CA) was performed on 19 critically ill patients with 2009 H1N1 influenza A pneumonia. The most severely ill group of 12 patients demonstrated impaired expression of numerous genes participating in adaptive immune responses (e.g., diminished antigen presentation, B-cell development, T-helper cell differentiation, and apoptosis), suggesting impaired adaptive immunity in severe viral pneumonia (55). In terms of epigenetics, many postulate that long-term epigenetic changes following severe pneumonia are responsible an increased likelihood of later infections and death, although specific epigenetic changes are yet to be identified (54).

VACCINATION AS PREVENTION AND POTENTIAL TREATMENT OF VIRAL PNEUMONIA

Natural infection with viral causes of pneumonia does not induce long-term protective immunity due to an evolutionary advantage allowing viruses to evade host immune defenses via antigenic shift and drift. Antigenic drift occurs with small point mutations in the viral genome leading to minor changes in key viral epitopes, while antigenic shift is a major change in a key gene leading to a complete exchange of a key epitope (56). Antigenic shift often leads to influenza epidemics secondary to vaccine strain-circulating strain mismatches. Antigenic shift is the molecular mechanism by which novel influenza strains emerge and is the cause of pandemics such as the 2009 H1N1 pandemic (57–61).

Influenza vaccines rely on conserved antigens such as ectodomain of influenza M2 protein, M2e, or hemagglutinin stalk domains. Hemagglutinin globular head specific antibodies confer immunity since it interferes with virus attachment to host cell receptors; however, they are also one of the most variable viral antigens (56). Additional adjuvants are important in vaccine

formulations to induce desired immune responses that would not be triggered with the antigen alone (62). The need for adjuvants in vaccinations confers an additional important role for DAMPs and PAMPs in viral immunity. One recent study used PAMP TLR9 agonist and commonly used pharmaceutical additive to induce the release of DAMPs to improve immunogenic response to the seasonal influenza vaccine (63).

Prevention of viral pneumonia is mainly limited to influenza vaccines since the formalin-inactivated RSV vaccine in the 1960s failed secondary to adverse events (64). However, oral adenovirus vaccination has been used in military populations with 100-fold reduction of respiratory illnesses (65, 66). Production of this vaccine was stopped in 1999 but was reintroduced in 2011, leading to a dramatic and sustained decrease of acute respiratory distress outbreaks among U.S. Army trainees (67, 68).

Additionally, there is still ongoing work to develop a vaccine to prevent RSV infection. Recently, one study reported protective immunity against RSV with a molecularly adjuvanted adenovirus serotype 5 based RSV oral vaccine in a rat model (69). However, two recent randomized control failed to establish an effect of anti-RSV monoclonal antibodies and recurrent wheeze of early childhood or asthma (70–73).

IMPLICATIONS FOR COVID-19

Clinical Presentation

Since the COVID-19 caused by the novel coronavirus known as SARS-CoV-2 began its rapid spread in Wuhan, China, in November 2019, researchers have responded swiftly to help thwart the pandemic by quickly establishing studies to better understand the virus. SARS-CoV-2 is a novel beta-coronavirus that likely originated in bats. The virus uses a glycosylated spike protein to bind to and enter the human host cell predominantly via angiotensin-converting enzyme 2 receptors that are highly expressed in type 2 alveolar cells (74).

The clinical presentation of COVID-19 can be indistinguishable from other viral causes of pneumonia and include fever (83–98%), dry cough (76–82%), and fatigue or myalgia (11–44%) (74, 75). The median age of confirmed COVID-19 cases is in the 6th decade of life with a slight male predominance. Twenty-five percent of patients have severe symptoms requiring intensive care treatment of which 10% develop respiratory failure requiring mechanical ventilation. Chest radiograph imaging of these patients reveals bilateral patchy infiltrates and CT imaging shows ground-glass infiltrates. Patients typically present with laboratory findings of prolonged prothrombin time, elevated lactate dehydrogenase, and lymphopenia (70% of patients) (76). However, it is unclear if the lymphopenia is related to direct cytotoxic effect of the virus or underlying chronic conditions (77, 78).

There are limited publications on the autopsy results of patients who have died from COVID-19. However, pathologic samples show hyaline membrane formation, interstitial mononuclear inflammatory infiltrates, and multinucleated giant cells. There are also high levels of pro-inflammatory cytokines, such as IL-2 and TNF-α. As with other causes of severe viral pneumonia, a "cytokine storm" occurs which also contributes to the high morbidity and mortality (79, 80).

Principles of Early Management

The most important aspect of early management of viral spread has been early isolation of those presenting with concerning symptoms, history, and high likelihood of exposure to prevent spread of the disease to those in immunocompromised states, the elderly, and/or those with comorbid conditions. A chest radiograph along with throat and mid-turbinate nasal swabs for respiratory viral panel (reverse transcriptase-polymerase chain reaction) are needed for proper diagnosis of COVID-19. Among hospitalized patients, negative pressure rooms and airborne-droplet-contact precautions are important for prevention and further spread between patients and hospital care-workers (81).

Currently, there is no approved drug or vaccination for the treatment or prevention of SARS-CoV-2 viral pneumonia. There are many trials underway attempting to attenuate the disease with remdesivir, IL-6 receptor blockers, IL-7, and antiretrovirals such as lopinavir-ritonavir (82). The *New England Journal of Medicine* recently published a randomized controlled trial evaluating the efficacy of lopinavir-ritonavir versus standard care alone in the treatment of adult hospitalized patients with severe COVID-19. There were no differences in hospital mortality, time to clinical improvement, or viral RNA levels. Although the median time to improvement was 1 day shorter with lopinavir-ritonavir on intention-to-treat analysis, 14% of patients had adverse events requiring treatment discontinuation. Therefore, it was concluded that there was no benefit observed with lopinavir-ritonavir treatment versus standard treatment of severe COVID-19 patients (83). Historically, hydroxychloroquine, an anti-malarial and anti-inflammatory agent, has shown some promise in reducing mortality from SARS and, therefore, is currently being studied for COVID-19 (84). In one very limited study from France (n = 20 per group, nonrandomized), hydroxychloroquine was associated with reduced viral load and reduced duration of viral detection which was further attenuated by the addition of azithromycin (85).

Research is already underway to create a vaccine to protect against SARS-CoV-2. Taking advantage of the similarities in structure between SARS-CoV (responsible for the 2003 SARS epidemic) and SARS-CoV-2 (responsible for COVID-19), studies have mapped several epitopes to be targeted for a potential vaccine (86, 87). WHO estimates an approximately 18-month timeframe for COVID-19 vaccine availability.

Until such time that effective therapies and vaccines become available, public health efforts should continue to focus on mitigating the spread of SARS-CoV-2 through well-established infection control strategies (88). This can be aided in the hospital with admission of SARS-CoV-2 positive patients into negative pressure rooms with contact precaution protocols requiring personal protective equipment such as gowns, gloves, fit-tested N95 respirators, and face shields. Additionally, rules limiting the people entering the isolation room and requiring logging of healthcare workers involved in COVID-19 patient care should be followed to effectively monitor patient contact and limit spread. All equipment (monitors, etc.) in the isolation room should be designated for the case patient only. Physicians should limit potential spread by recognizing any necessary aerosol-generating procedures and preparing accordingly (e.g., for intubation using controlled measures including paralytics, video laryngoscopy, N95 masks).

Although fomites are suspected as the main source of transmission, there is also possible fecal-oral transmission; therefore, hand washing is a mainstay of control/prevention (89).

CONCLUSIONS

Although viral pneumonia is common, the specific inflammatory and immunosuppressive effects it has on the host is still largely unknown. COVID-19 has brought viral pneumonia and subsequent host pathology to the forefront of medical care and research. SARS-CoV-2 spread worldwide in a matter of months to cause a pandemic not seen since influenza in 1918. Our highly interconnected global society creates ample opportunity for the rapid spread of novel viruses. Since these types of viral pandemics have occurred multiple times historically (e.g., influenza in 1918, Middle East respiratory syndrome in 2014, and SARS in 2004) and will continue to occur in the future, research into immunomodulative therapies for patients afflicted with viral pneumonia will be a key aspect to improving outcomes after viral pneumonia. A personalized approach, taking into account differences in the biology of individuals and the pathophysiology of different viruses, will also be required to make significant progress in the treatment of these patients.

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